INSTITUTE: National Institute of Child Health and Human Development

STUDY NUMBER: 00-CH-0160 PRINCIPAL INVESTIGATOR: Constantine Stratakis, M.D.

STUDY TITLE: Clinical and Molecular Analysis of ACTH-Independent Steroid Hormone Production in Adrenocortical Tissue

Latest IRB Review: Continuing Review 7/23/04
Latest Amendment Approved: Amend D 4/8/03
Adult Patient

INTRODUCTION

We invite you to take part in a research study at the National Institutes of Health (NIH).

First, we want you to know that:

Taking part in NIH research is entirely voluntary.

You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled. However, to receive care at the NIH, you must be taking part in a study or be under evaluation for study participation.

You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your NIH doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at NIH, or with family, friends or your personal physician or other health professional.

You or your child are being asked to participate in this study because of the presence of a tumor in one of the glands of the human body that produce hormones, called the "adrenal gland". Normal individuals have two adrenal glands, one on each side of the body, and tumors can form in one gland only, or can involve both glands. These glands normally secrete many different types of steroid hormones, each of which has a different role in the body's normal function. Sometimes tumors of the adrenal gland secrete hormones and sometimes they do not. The causes of these tumors are unknown, and it is also not known why some secrete hormones and some do not. Sometimes these tumors can run in families, in which case they are often associated with tumors in other glands. Some adrenal tumors are "benign", meaning that they do not spread within the body. These tumors are also known as "adrenal adenomas". The other type of adrenal tumor is a "malignant" tumor, meaning that it can spread to other places in the body. A tumor of this type is sometimes called an "adrenal carcinoma".
The purpose of this study is to investigate why some adrenal gland tumors secrete hormones, and also to try to determine what makes an adrenal tumor "benign" or "malignant". At the National Institutes of Health, we will

determine what hormone the adrenal tumor is secreting, and this investigation will not be different from a standard medical evaluation of an adrenal tumor. The research portion of this study is related to finding out if the adrenal tumor can be made to secrete the steroid hormone in response to a variety of specific tests. This part of the research will involve approximately 1 (one) week of testing, which will be performed on the inpatient Endocrine ward of the Clinical Center of the National Institutes of Health. When we have studied the effects of these tests on the tumor, participants in the study will have the adrenal tumor surgically removed at the NIH. For most (if not all) adrenal tumors, surgical removal is the standard treatment that would be recommended at other hospitals in this country.

What is this study about?

The purpose of this study is to study how adrenal tumors develop and why some of them secrete steroid hormones.

What is regular medical care and what is research in this study?

I. Routine Medical Care

In order to make a recommendation for treatment of you or your child's adrenal tumor, we may need to do a number of blood, urine and X-ray tests. We will not repeat any of the tests that have already been performed, unless there is a need to do them because a long time has passed since they were performed or because their results were unclear.

If a diagnosis of cortisol oversecretion (Cushing syndrome) has been made, it will be necessary to verify that the disease is being caused by an adrenal tumor. To establish the diagnosis of Cushing syndrome, an individual referred for this diagnosis will need to have documentation of elevated cortisol, either by salivary or urinary free cortisol measurements. In order to establish the adrenal nature of the problem, each participant in the study will have a baseline ACTH measurement and a dexamethasone suppression test. If these investigations have been obtained prior to referral to the NIH, documentation of these results will be sufficient.

Likewise, patients referred with a diagnosis of hyperaldosteronism will require measurement of the aldosterone-renin ratio and dynamic test confirming the presence of the adrenal origin of the condition (e.g., saline suppression test). Some patients who present with hyperaldosteronism will have overproduction of this hormone by both adrenal glands (known as "bilateral hyperplasia"), which can be seen even when one gland appears to have a tumor. To check for this possibility, we may recommend a special procedure where blood is taken directly from the veins that drain the adrenal glands and aldosterone is measured. If indicated for clinical reasons, this procedure will be performed by a specialist who will explain the procedure in detail and ask you to sign an additional consent form.

Once the diagnosis of an adrenal hormone secreting tumor has been confirmed, plans will be made to have the tumor surgically removed at the NIH by an experienced adrenal surgeon and his team. The only exception to this would be in the situation just described where there is overproduction of the hormone aldosterone by both adrenal glands. In that case, treatment with medications is usually recommended.

All participants in the protocol will be asked to return to the NIH approximately one (1) year after the time of surgery for an outpatient follow-up visit at the NIH Endocrinology Outpatient clinic, at which time we will do testing to verify that your adrenal gland function has returned to normal. During this first year following surgery, you and your regular doctor may wish for some assistance in managing your adrenal hormones. If this is the case, we will most likely be able to see you in the outpatient clinic for this purpose. If we are not able to tell at the time of surgery if your tumor is

benign or malignant, we will ask you to return to the NIH every year as long as this protocol is in effect up to a maximum of five (5) years. During all of this follow-up period, it will be necessary for you to have a local endocrinologist caring for you in the event of urgent problems. Following this time or after your (or your child's) discharge from the hospital the first time (if you do not wish to be followed by our clinic), we will make suggestions and, if possible, arrangements for follow up elsewhere.

No tests, other than the ones described below in the "research" section, will be obtained for research purposes only during your (or your child's) stay in our hospital. If you wish, however, to participate in other research studies performed at the NIH, please let us know, either before your admission to the hospital or during your stay here.

II. Research Components of the Study

The research components of this study have the following objectives:

• To determine if the tumor can be made to secrete hormones in response to stimuli that should not normally cause the adrenal gland to secrete hormones.

• To examine the tumor tissue to look for abnormal receptors that might cause the tumor to respond to abnormal stimuli. This part of the study will only include those individuals who require surgery for standard treatment of the tumor. The type of tumor will be verified when the tumor is taken out at surgery and the tissue is examined in the laboratory. The tumor will also be studied in the laboratory to see if specific changes can be detected that will predict which tumors will behave as benign or malignant.

• For cases in which adrenal tumors appear to run in the family, we will collect an extra tube of blood to purify DNA. DNA is the substance that contains the genes, the units that determine inheritance. If we think that a disease that makes your child more likely to have tumors runs in your family, we will ask you to help us draw a family tree and collect blood from you and your relatives. We will compare the DNA from various family members to see if we can find something in common among the people who have tumors. This will help us to find the problems in these genes.

What we will do

We will contact you by phone or mail, after your endocrinologist has told us about your (or your child's) disease. We will discuss with you and your physician whether you are eligible for the study.

All individuals that elect to participate in this study will be admitted to the hospital for the needed testing. This hospitalization will last approximately 7-10 days. After that time, we will discuss with you a plan for further treatment. If surgery is recommended (as it is in most, if not all, cases), we will arrange with you and the surgical team a date for the surgery. In some cases, the surgery can be performed during the same hospital admission; at other times, a brief discharge and readmission may be required.

Once admitted to the hospital, we will do the following:

(1) Medical history: We will ask you about medical conditions associated with diseases of the adrenal gland. These may include high blood pressure, diabetes, strength, and memory. We will also inquire about conditions that may be related to familial syndromes associated with adrenal tumors, including skin problems and tumors in other parts of the body. We may ask you to help us draw a "pedigree" (this is a medical term for a special diagram of your family tree).

We may also ask for additional medical records for problems that you (or your child) have had in the past, and we may need to contact the physicians that took care of you then. We will ask you to sign a paper to allow us to see these records.

(2) Physical examination: We will perform a complete physical examination, including body measurements as appropriate. For children and adolescents, the examination will include specific measurements ("Tanner staging") to determine the extent of sexual maturity, including examination of the genital area. Women will also be examined for evidence of abnormal hair growth ("Ferriman-Galway score").

(3) We may ask you to collect urine over twenty-four or more hours, to measure hormones in the urine.

(4) Blood testing: To see if your adrenal tumor secretes hormones in response to abnormal stimuli, you will undergo a series of stimulation tests. In general, you will be challenged with a specific stimulus (which may be exercise, food, an IV medication, or a pill), and blood will be withdrawn every 30 minutes for up to 3 hours in order to examine the effect of that test on the secretion of hormones. In order to make these tests less stressful, a small plastic tube (intravenous catheter, or "IV") will be placed in the arm before the beginning of all of the tests. This will be used to give most of the test stimuli, and will also be used for withdrawing all of the blood.

The research tests that are planned for all participants in the protocol are as follows:

i) 2 hours of standing/walking. Patients will be asked to refrain from sitting or lying down for 2 hours. They may stand or walk freely during the test. There are no specific risks associated with this test, although some individuals may feel lightheaded or weak after standing for 2 hours.
ii) A mixed meal test. Patients will be given a standard meal consisting of a mix of protein, carbohydrate, and fat. Again, there are no specific risks associated with this test. Please inform the physicians prior to admission if you have any specific dietary requirements.
iii) An adrenocorticotropin (ACTH) stimulation test.
iv) A luteinizing hormone releasing hormone (LHRH) stimulation test.
v) A thyrotropin releasing hormone (TRH) stimulation test
vi) A growth hormone releasing hormone (GHRH) stimulation test.
vii) A Glucagon stimulation test.
viii) A Vasopressin stimulation test.

For tests iii) - viii), patients will be given an injection of the appropriate hormone in the vein through the IV catheter.

Each of these substances is a normal human hormone that is found in the body. Each of these tests has been associated with side effects such as headache or flushing. There is also the chance of a severe allergic reaction to these substances. However, this is unlikely because all of these are normal human hormones. In the event of such a reaction, you will be in the hospital and therefore will be treated immediately as needed.

There have also been associations that are specific to each one of the above tests. These specific risks are listed below:

- For the TRH, ACTH and LHRH tests:

Especially with the TRH (and less frequently with the others) tests, bleeding of the pituitary gland has occurred, but only in individuals shown to have a pre-existing pituitary tumor. To prevent this occurrence, all individuals will have an MRI examination of the pituitary gland *prior* this regimen of tests to rule out the presence of a pituitary tumor. If a tumor exists, these tests will not be done.

- For the vasopressin test:

Administration of the hormone vasopressin has been associated with changes in blood pressure and heart trouble when given in though the vein in high doses. We do not anticipate you to have any heart problems, because we are giving you a single, small dose of this medicine. However, if there is a suspicion that you may be at risk, a cardiology consultation will be obtained at the NIH before proceeding with this test.

Based on the results of this testing, it may be desirable to perform an additional 2-4 series of blood tests to check for a hormone response to other specific stimuli. These tests will be carried out in the same way as the first set, and may involve giving you additional hormones either through the vein (such as luteinizing hormone or follicle stimulating hormone) or by mouth (such as thyroid hormone). These extra tests might also take the form of a special type of meal, or possibly an infusion through the vein of a salt solution. We may also wish to give you an infusion through the vein of a medicine called isoproteronol. This medicine has been shown to cause heart attacks when given at very high doses over 1-2 days. The doses that have caused these problems are more than 10 times higher than what we will be using, and we will be only giving you this medicine for 30 minutes. At the doses that we use, many people get a rapid heart beat and a small increase in blood pressure, but that is all. If any of these tests are felt to be necessary, the details and any potential side effects will be discussed with you prior to carrying them out. If you and your doctors feel that the test would pose too much of a risk to you, it will not be done. Also, if you have had a bad reaction to one of the tests described above, please notify your NIH physicians prior to any potentially dangerous testing.

(5) X-ray and other studies: A non-x-ray scan (MRI) of the head that includes the pituitary gland will be obtained, if you (or your child) has not had one recently. Because the MRI requires that the subject lay still during the test, some children require sedation for the procedure, and this sedation carries a slight additional risk. If sedation is necessary, an anesthesiologist will explain the risks and benefits to you, and ask you sign a separate consent form. Other studies, such as a computed tomography (CT) of the adrenal glands may be need to be obtained, if not already done. In both tests, a dye ("contrast" material) may need to be given through a vein. This procedure will be explained to you in detail by the doctor who will be doing it (a radiologist) and a separate consent will be obtained.

(6) We may ask your permission to take photographs of your condition as a means of documenting the effects of the adrenal tumor. Photography is frequently done by endocrinologists to demonstrate the effects of abnormal hormone secretion. These pictures will not be used for any publication without your written permission.

(7) Material used for research

From the same tube (the "catheter"), we may get a small amount of blood [about 2 tablespoons (30 (8ml)] for genetic analysis. We will use this to get DNA.

We will also be using part of the tissue from the tumor that will be obtained during surgery.

Tissue from the adrenal tumor specimen will be used in the laboratory for establishment of a culture system that may be transplanted in animal models by associate investigators of this study. This experiment will allow us to learn more about what forms a tumor in the adrenal glands and how to treat it in the animal model and, perhaps, later in the human.

(8) Creation of a patient registry

Because adrenal tumors are uncommon, we would like to maintain a list (called a "registry") of all people who participate in this research study. We will use this list in order to maintain appropriate records of the patients seen at the NIH and also to correlate the medical histories with any tissues that are kept at the NIH. We may periodically contact you after the completion of the study to see if there have been any changes in your medical condition. Keeping the registry will also allow us to inform you of any new studies that may be of interest to you. The registry will not be made accessible to individuals/organizations outside the NIH.

(9) Follow up after the completion of all medical studies

After all the medical testing, several options will be discussed with you. We will report the results of the medical tests to you and your doctor.

To decide how the adrenal tumor should be treated, your (or your child's) case will be presented to our surgery service. If the medical and surgical teams decide that surgery is the best treatment option for the tumor, we will discuss it with you, and recommend surgery here at the NIH. In many cases, the surgery can be done through 4 small holes in the abdomen or flank ("laparoscopic surgery"). If the tumor is very large or there is a suspicion that the tumor may be malignant, the surgery may be done through a standard surgical incision. The surgeons will explain the details of the planned surgery to you. Separate consent will then be obtained for this. If a surgery is not successful, repeat surgery may need to be done. This will be discussed with you by the surgeon and us. Complications of the surgery are briefly listed in the "risks" section of this consent form; however, they will be extensively discussed with you by us and the surgeon. Surgery is not always able to cure a tumor. Individuals with malignant tumors that cannot be cured by surgery may be candidates for chemotherapy or for radiation treatment but this is not offered at the NIH under this research protocol. Individuals receiving treatment at the NIH under this protocol may be eligible for continued treatment at the NIH under a different protocol (for example, a protocol at the National Cancer Institute). If appropriate, referrals to such protocols will be made at the direction of the patient.

For the medical treatment and the follow-up after surgery, you can be seen as an outpatient at the NIH Clinical Center Endocrinology Outpatient Facility for the first year after your surgery. For individuals with certain types of tumors, it will be possible to continue NIH follow-up on an annual basis (i.e., once per year) as long as the protocol is active for up to five years. Your ability to get follow up at the NIH for this extended period of time will be discussed with you before the time of discharge after the adrenal surgery. Before, or at the end of the follow-up period, at your request, we will make arrangements for the continuation of your (or your child's) care by your local physician or endocrinologist.

(10) Alternatives to treatment provided at the NIH

The evaluation and treatment that will be performed at the NIH can be found at other hospitals.

At any time after entry into the study, you may decide to stop coming to the NIH. We will provide you with all the information gathered here about your (or your child's) health and talk to the physicians wherever you may decide to

go, to ensure proper follow-up treatment. Please let us know, at any point, of concerns you might have, or of any questions that may arise.

If you decide to go somewhere else for treatment, you can still participate in this study, by allowing us to contact the doctors that will be taking care of your or your child and make arrangements for us to receive part of the tumor tissue that will be taken out.

Other risks or discomforts from participation in this study

1. Some people feel it is inconvenient to give information about medical and family history, and to have physical examination and any testing needed to find out about the adrenal tumor.

2. Total blood drawing will not exceed the NIH safety limit.

Blood drawing can be uncomfortable too; this includes the pain of the needle-stick, the slight chance of fainting, the possibility of a bruise, and the small chance of an infection at the needle puncture site. You will receive appropriate treatment for any complications of this sort.

There may be additional risks from the medical tests that will be obtained here at the NIH; these will be explained to you in detail, if such a test becomes clinically indicated. They include headaches, blood pressure changes, rashes due to allergy, and other symptoms. During the testing, patients are closely monitored for any symptoms suggestive of a medical difficulty. Treatment will be offered immediately in such an event.

3. Patients in this study will have an MRI that they would most likely not have at an outside institution. MRIs may be hazardous to individuals with a history of exposure to metal chips which can lodge unknowingly in the eye (e.g., welders). If this condition may apply to you, please notify your doctor so that a precautionary X-ray can be performed. Also, some individuals experience anxiety about going into the MRI scanner, and sedation is sometimes required. Staying in the MRI room with all its noise and large equipment may be uncomfortable for young children, who, in addition, have to stay still for the proper completion of the procedure. Moreover, sedation has its own risks (respiratory and others) which will be explained to you by the anesthesiologist and radiologist that will be there during the procedure. If sedation is needed, the physician who will be administering it will obtain another consent form at the time of the procedure.

4. If surgery is needed, there are possible complications of the various procedures that may be performed, including infection, injury to the bowel or kidney and, rarely, death. These will be explained to you in detail by us and our surgeon in a separate consent form.

5. Lastly, a lot of articles have appeared recently in newspapers and magazines about "genetic testing" and health insurance.

The results of our study will be available to you and your referring physician; thus, they become part of the formal medical record, which is protected by "the Federal Privacy Act". We will not release any of this information without first getting your permission. However, this Act allows release of some information from your medical record without your permission, for example, if it is required by members of the Congress, law enforcement officials or other authorized people. Your or your child's ability to obtain insurance could be affected if our study results show a gene that causes

tumors is found in your or your child's blood. Theoretically, this could also make it harder to find a job, if an employer knew about the problem.

Although this is not part of our study, our DNA tests may indicate that the assigned paternity is in question. We will not investigate this in any way, and we will not reveal the results of this test to you or anybody else; we will not be using DNA samples with evidence for false paternity for any other studies. As stated elsewhere in this consent form, if we learn anything else about you or your child's medical condition during the course of this study, we will inform you and your doctor; the discovery of false paternity will not affect this course of action, and in this process, no such information will be provided.

Benefits

1. You will have the benefit of a thorough endocrine investigation, which may uncover previously unknown medical conditions that may be associated with adrenal tumors. Additionally, the surgery performed at the NIH will be done by highly experienced surgeons and the medical staff is very accustomed to treating patients with adrenal hormone abnormalities.

2. If you or your child does have a genetic condition associated with adrenal tumors, or if we discover that you are at risk for developing any of these diseases or their complications, we will discuss with you the chance that your other children or your child's children could have the same health problems. If appropriate, we will refer you for additional genetic counseling.

3. All participants in the study can receive appropriate medical or surgical treatment and follow-up for one year at the NIH, and may be eligible for up to five years of annual follow-up. During this follow-up period, NIH physicians will provide consultative care regarding the post-operative management of adrenal tumors to your local physician.

4. The knowledge derived from this study may give us a better understanding of adrenal tumors and other conditions associated with them, eventually leading to better treatments and better ways to detect or even prevent such tumors

OTHER PERTINENT INFORMATION

1. Confidentiality. When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

The Federal Privacy Act protects the confidentiality of your NIH medical records. However, you should know that the Act allows release of some information from your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or other authorized people.

2. Policy Regarding Research-Related Injuries. The Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the National Institutes of Health, the Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

3. Payments. The amount of payment to research volunteers is guided by the National Institutes of Health policies. In general, patients are not paid for taking part in research studies at the National Institutes of Health.

4. Problems or Questions. If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Constantine Stratakis, M.D.; Building 10, Room 10N262, Telephone: 301-402-1998.

You may also call the Clinical Center Patient Representative at 301-496-2626.

5. Consent Document. Please keep a copy of this document in case you want to read it again.

COMPLETE APPROPRIATE ITEM(S) BELOW:

A. Adult Patient's Consent
I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study.

Signature of Adult Patient/Legal Representative _____ Date _____

B. Parent's Permission for Minor Patient.
I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby give permission for my child to take part in this study.
(Attach NIH 2514-2, Minor's Assent, if applicable.)

Signature of Parent(s)/Guardian _____ Date _____

C. Child's Verbal Assent (If Applicable)
The information in the above consent was described to my child and my child agrees to participate in the study.

Signature of Parent(s)/Guardian _____ Date _____

THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM JUNE 23, 2004 THROUGH JUNE 23, 2005.

Signature of Investigator _____ Date _____ Signature of Witness _____ Date _____